A Transplant Center's Experience with Orthotopic Liver Transplantation Outside of the Milan Criteria: Is Expansion of Current Allocation Criteria Justified?

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A. Title:

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B. Lay Abstract:

Hepatocellular carcinoma (HCC) is an aggressive cancer that occurs in the liver. It is the fifth most common cancer in the world and the third most common cause of cancer-related death. Several risk factors exist for HCC, including Hepatitis B virus, environmental toxins, Hepatitis C virus, hereditary hemochromatosis, and cirrhosis [1] [2] [3]. There are more than 500,000 new cases of HCC diagnosed every year [4]. As a result, the prevention and treatment of HCC are active areas of research. There are many treatment options available for patients with HCC [1] [3]. Surgical resection is the optimal treatment, but many patients are not candidates for resection because of their tumor burden and/or underlying liver dysfunction [5] [6]. For these patients, liver transplantation is among their other treatment options.

The Milan criteria were established in 1996 [7], indicating which patients with HCC, in terms of their tumor burden, would stand to benefit from liver transplantation. These criteria have been accepted by the United Network for Organ Sharing and used to determine priority for donor liver allocation [8] [9]. In recent years, there has been considerable interest regarding the expansion of these allocation criteria [10] [11] [12] [13] [14] [9] [15]. Expansion would allow more patients with HCC to have access to potentially curative liver transplantation. A suggested expansion of the criteria, known as the UCSF criteria, has been shown to result in comparable outcomes to the Milan criteria [12].

The main purpose of this study is to examine our transplant center's experience with patients who have undergone liver transplantation for HCC. We are interested in comparing the outcomes between patients who meet the Milan criteria with those that exceed the Milan criteria but fulfill the UCSF criteria. Through this study, we hope to yield additional information that may aid in the consideration of expanding the current Milan criteria used in donor liver allocation.

C. Study Purpose and Rationale:

Hepatocellular carcinoma (HCC) is an aggressive primary tumor of the liver. It is the fifth most common neoplasm in the world and the third most common cause of cancer-related death. A variety of risk factors have been identified for HCC, including hepatitis B virus, environmental toxins, hepatitis C virus, hereditary hemochromatosis, and cirrhosis [1] [2] [3]. As there are more than 500,000 new cases of HCC diagnosed yearly [4], the prevention and treatment of HCC are areas of great research interest.

Several treatment modalities are available for patients who have HCC [1] [3]. These include: surgical resection (partial hepatectomy), liver transplantation (LTX), radiofrequency ablation (RFA), percutaneous ethanol or acetic acid ablation, transarterial chemoembolization (TACE), cryoablation, radiation therapy, and systemic chemotherapy. Potentially curative partial hepatectomy is the optimal treatment for HCC [5] [6]. However, many patients with HCC are unable to undergo surgical resection because of tumor extent and/or underlying liver dysfunction. These patients must then consider other treatment options, such as LTX.

A study conducted by Mazzaferro, et al., in 1996 has established LTX as a potential treatment option for HCC [7]. In this study, it was shown that when transplantation was restricted to patients with early HCC, three- to four year-actuarial survival rates of 75-85 percent and recurrence-free survival rates of 83-92 percent could be achieved. These outcomes are similar to the expected survival rates for patients who are undergoing transplantation for non-malignant indications. Early HCC is defined by Mazzaferro, et al., as a single lesion less than or equal to 5 cm, up to three separate lesions none of which is larger than 3 cm, no evidence of gross vascular invasion, and no regional nodal or distant metastases [7]. These criteria are known as the Milan criteria and have been widely applied in the selection of patients with HCC for LTX.

Typically, the United Network for Organ Sharing (UNOS) uses the Model for End-Stage Liver Disease (MELD) to determine priority for the allocation of liver allografts for LTX [8]. The MELD is a prospectively developed and validated chronic liver disease severity scoring system that uses a patient's laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival. The MELD was officially adopted by UNOS as the basis for cadaveric liver allocation for adult patients (greater than or equal to 18 years of age) in February of 2002.

However, for patients with HCC, the traditional MELD system is not very useful. Compared to patients who suffer from other non-malignant liver diseases, many HCC patients have minimal liver dysfunction. Also, the waiting period for LTX can be as long as 1-2 years, which may lead to tumor growth or progression of underlying liver disease in HCC patients. As a result, HCC has been established as a MELD exception in LTX selection. Currently, the Milan criteria are accepted and used by UNOS rather than the traditional MELD criteria for organ allocation in patients with HCC [8] [9]. Higher priority MELD scores are assigned to HCC patients based upon their tumor burden. These scores are then increased every three months until LTX occurs.

Unfortunately, even with higher priority MELD scores, HCC patients may still have to wait as long as one year for a donor liver allograft [9]. As a result, these patients still remain at increased risk for tumor growth. Tumor growth may lead them to have tumors that are beyond the Milan criteria. Thus, during their wait-time, these patients, though originally suitable for LTX, may find themselves becoming disqualified from LTX. In addition, despite the existence of exceptional status for patients with HCC, many patients are not eligible for LTX at the time of

their HCC diagnosis, because of their tumor extent (i.e. outside of Milan criteria), their underlying liver dysfunction, and the lack of donor organs [9].

Given the current shortage of donor livers, at certain transplant centers, many patients with HCC that is outside of the Milan criteria may be eligible for receipt of extended-donor criteria (EDC) liver allografts. These liver allografts do not meet traditional criteria for transplantation. Indications for EDC designation may include: age>65yrs, macrosteatosis>20%, cold ischemic time>12hrs, hypernatremia>155meq/l, donation after cardiac death, CDC high-risk behavior, hepatitis B, C, or human T-cell leukemia viral serology, and donor history of cancer [16] [17]. A study conducted by Renz et al that examined the utilization of EDC liver allografts found that the use of EDC liver allografts increased patient access to LTX and reduced pre-LTX mortality [16] [17].

Recently, these issues have led to considerable interest in the expansion of the Milan criteria that is currently used in liver allocation [12] [10] [18] [11] [13] [14] [9] [15]. Expansion of the Milan criteria may allow more patients with HCC to have access to potentially curative LTX. Many of these proposals for criteria expansion are based upon tumor size and number [19] [12] [10] [18] [11] [13] [14]. In a study conducted by Yao et al at the University of California at San Francisco [12], it was shown that patients selected for LTX using expanded eligibility criteria experienced outcomes that were comparable to those of patients meeting the Milan criteria. Their expanded eligibility criteria, also known as the UCSF criteria, is as follows: a single HCC nodule up to 6.5 cm, or with up to 3 lesions, the largest less than or equal to 4.5 cm and the sum of the diameters less than or equal to 8 cm.

The main purpose of this study is to examine our center's experience with patients who have undergone LTX for HCC between the years 1998 and 2005. The survival rates of two different groups of LTX patients will be compared. These groups include: (1) HCC patients who fulfill the Milan criteria and (2) HCC patients who exceed the Milan criteria but fulfill the UCSF criteria. Through this study, we hope to yield additional information that may aid in the consideration of expanding the current Milan criteria used in donor liver allocation.

D. Study Design and Statistical Analysis:

This will be a retrospective cohort study of the impact of the expansion of current liver allocation criteria for HCC patients on patient outcome. Previous studies have shown that an expansion of the currently used Milan criteria to the UCSF criteria may result in comparable survival rates and allow more HCC patients to have access to potentially curative LTX. Specifically, in this study, we will be examining our center's experience with patients who have undergone LTX for HCC. Outcomes will be compared for two different groups of patients who have undergone LTX for HCC during the time period of 1998 to 2005. These groups include: (1) Patients who fulfill the Milan criteria and (2) Patients who exceed the Milan criteria but fulfill the UCSF criteria.

Approximately 330 adult patients (18 years of age or older) underwent LTX for HCC at the Center for Liver Disease and Transplantation (CLDT) at the Columbia Presbyterian Medical Center (CPMC) during the years 1998 to 2005. Of these 330 patients, 12 patients were outside of the UCSF criteria and, thus, ineligible for the study. Of the remaining 318 patients, 177 patients fulfill the Milan criteria (Group A) and 141 patients exceed the Milan criteria but fulfill the UCSF criteria (Group B). The Milan criteria require that the patient's HCC be restricted to either a single lesion less than or equal to 5 cm, or up to three separate lesions none of which is larger than 3 cm. There may also be no evidence of gross vascular invasion and no regional nodal or distant metastases. The UCSF criteria are: a single HCC nodule up to 6.5 cm, or with up to 3 lesions, the largest less than or equal to 4.5 cm and the sum of the diameters less than or equal to 8 cm.

The primary outcome evaluated in this study will be a composite survival rate for each group of patients. Patient survival, graft survival, and recurrence-free survival will be included in this composite survival rate. Patient survival can be defined as whether or not the patient was still alive post-LTX. Graft survival can be defined as whether or not re-transplantation was required during the post-LTX period. Recurrence-free survival can be defined as whether or not the patient was noted to have recurrence, either a new primary tumor in the liver or metastases elsewhere, during the post-LTX period. This information will be obtained via a retrospective chart review of patient medical records.

Past studies have indicated that patients who undergo LTX with HCC that fulfills the Milan criteria have survival rates of approximately 75%. Given that we are limited to a study population of 318 patients, of which there are 177 patients who fulfill the Milan criteria and 141 patients who exceed the Milan criteria but fulfill the UCSF criteria, a Chi-square test was performed to determine the detectable effect size. With an alpha of 0.05 and a power of 0.8, Chi-square analysis indicates that we would be able to detect a maximal survival rate of 60% in those patients who exceed the Milan criteria but fulfill the UCSF criteria.

E. Study Procedures:

None

F. Study Drugs:

None

G. Medical Device:

None

H. Study Questionnaires:

None

I. Study Subjects:

330 adult patients (18 years of age or older) have undergone LTX for HCC at the Center for Liver Disease and Transplantation (CLDT) at the Columbia Presbyterian Medical Center (CPMC) between the years 1998 and 2005. Of these 330 patients, 12 patients had HCC that exceeded the UCSF criteria and are, thus, ineligible for the study. The remaining 318 patients will make up the study population that will be evaluated. All of these patients have received their pre- and post-LTX treatment and care at the CLDT. Patients were diagnosed as having HCC via serum alpha-fetoprotein (AFP) level, liver biopsy, or imaging studies (MRI, CT, Angiography). The extent of their tumor burden (tumor size, tumor number, gross vascular invasion, regional nodal or distant metastases) was assessed pre-LTX via routine radiological imaging (MRI or CT), angiography, or exploratory laparotomy. Patients may have also undergone surgical resection, TACE, RFA, or systemic chemotherapy pre-LTX. At LTX, these patients either received standard MELD-allocated liver allografts or EDC liver allografts. All patients included in the study have had at least a minimum of one year of follow-up evaluation at the CLDT.

Of the 318 patients being evaluated in this study, 177 patients fulfill the Milan criteria (Group A) and 141 patients exceed the Milan criteria but fulfill the UCSF criteria (Group B). These patients were sorted into these two different groups based upon their tumor burden pre-LTX. The Milan criteria require that the patient's HCC be restricted to either a single lesion less than or equal to 5 cm, or up to three separate lesions none of which is larger than 3 cm. There may also be no evidence of gross vascular invasion and no regional nodal or distant metastases. The UCSF criteria are: a single HCC nodule up to 6.5 cm, or with up to 3 lesions, the largest less than or equal to 4.5 cm and the sum of the diameters less than or equal to 8 cm.

J. Recruitment of Subjects:

Potential subjects were identified via a retrospective chart review of all patients who have undergone LTX at the Center for Liver Disease and Transplantation (CLDT) here at the Columbia Presbyterian Medical Center (CPMC). Patients who underwent LTX for HCC will be identified. Only those patients who underwent LTX for HCC between 1998 and 2005 were included in this study.

K. Confidentiality of Study Data:

Data will be obtained from electronic medical records (WebCis), which are protected by pre-existing privacy mechanisms. All data that is collected for this study will be coded with a unique code number established for all study subjects. Data will be de-identified, and maintained in a database on a password-protected computer. The computer will be located in the office of the Principal

Investigator and locked during non-business hours. Data will be accessible only to the investigators involved in this study.

L. Potential Conflict of Interest:

None

M. Location of the Study:

The Center for Liver Disease and Transplantation (CLDT) at the Columbia Presbyterian Medical Center (CPMC).

N. Potential Risks:

None

O. Potential Benefits:

None

P. Alternative Therapies:

None

Q. Compensation to Subjects:

None

R. Costs to Subjects:

None

S. Minors as Research Subjects

None

T. Radiation or Radioactive Substances

None

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